The particle size of droplet, viscosity, physical properties of interface and critical micelle concentration could affect the formulation of a stable non-aqueous emulsion. However, with the attractive features of a non-aqueous emulsion system, a challenge remains for thermodynamically stable non-aqueous emulsions for further development to be applied in the pharmaceutical field. Non-aqueous emulsions have been used for oral and topical drug delivery, protein and peptide drug delivery, periodontal pocket delivery, controlled drug delivery and cosmetic application. These systems also have been filled in capsule or used as carrier for magnetite nanoparticles and prepared as the multiple emulsion.

Keywords: non-aqueous emulsion, development, pharmaceutical application

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Introduction

Although there are limited applications in the pharmaceutical field, the non-aqueous emulsion system could be applied in topical drug delivery system\(^1\) to prepare the nano– and micro- particles\(^2\), as a parenteral drug delivery system itself\(^3,4\) or in non-aqueous \textit{in situ} forming microparticle (ISM) systems.\(^5\) Non-aqueous emulsions may be used advantageously in pharmaceutical and cosmetic applications if they are composed primarily of edible, non-toxic ingredients and can be formulated to exhibit a wide range of suitable properties. Some usages includes the topical application bases for dermatological formulations, particularly for poorly-stable drugs or as emollient bases for various cosmetic preparations; for example, deodorants, skin cream, hair care products.\(^6\) It can used as nutrient preparations, drug reservoirs, or templates for the preparation of microspheres, nanoparticles and silicates microstructures.\(^7,8\) This review offers the role of physical properties in the development of non-aqueous emulsions. The evaluation and application of non-aqueous emulsion are also mentioned.

Role of physical properties in the development of non-aqueous emulsions

For development of the non-aqueous emulsions, there are the crucial factors that should be considered as following:

1. Critical micelle concentration

Typically, the surfactant molecules at low concentration disperses as monomer in solution because the entropy of mixing outweighs the attractive forces operating between the surfactant molecules. When the concentration of surfactant is increased, they can spontaneously aggregate into thermodynamically stable structure, which was occurred over a narrow range of concentration: the critical micelle concentration (CMC). Below CMC, surface-active agents are
preferentially adsorbed mainly at air-polar solvent interface as monomer. When surfactant monomers encounter the polar solvent environment, polar solvent molecules repel the polar-solvent insoluble hydrocarbon tail of amphiphiles. Therefore, the hydrophobic tails are directed away from polar-solvent, while the solvophilic heads are attracted by polar solvent by electrostatic attraction force. As the concentration of surfactant increases, the interface and the bulk phase become saturate with monomer.10

2. Particle size

As the globule size is reduced, they tend to exhibit Brownian movement. The diameter of globule is considered a major factor, which causes creaming of microemulsions. In general, the rate of creaming decreases fourfold when the globule diameter is halved. In microemulsions, the rate of creaming is insignificant; however, it is necessary to choose optimum globule size for maximum stability.10

3. Viscosity

Viscosity is a common strategy for the stability of an emulsion. As the viscosity increases, flocculation of globules is reduced because the Brownian movement of a globule is restricted. This decrease of mobility of globules eventually leads to creaming. Due to this undesirable effect, an optimum viscosity must be achieved for good stability.10 The stability of the non-aqueous emulsion can be enhanced by increasing the viscosity of the continuous phase. For the castor oil in silicone-oil emulsions, the viscosity of the silicone continuous phase was varied from 1 to 100 centipoises. With a non-ionic surfactant as the emulsifier, the optimal viscosity was found to be 48 centipoise. It is evident that there should be such an optimum as the energy required to produce small droplets is greater in liquids of the higher viscosity. On contrary, a continuous phase having a lower viscosity has a chance to cause creaming or settling of the emulsion.11

However, the viscosity of the emulsion should also be considered for the ease of injection to reduce the pain and provide patient compliance, especially in the injectable non-aqueous emulsion system of ISM. The presence of oil in the external phase may have an effect on the viscosity of the system. The previous study revealed that the trend of viscosity of ISM was similar with ISG but the viscosity of ISM was lower because of the presence of oil in the external phase12,13 that promoted the higher syringeability and to be easily administered. In addition, the hindrance effect of the oil phase affecting the ISM system.13

4. Physical properties of an interface

Emulsion systems have minimal thermodynamic stability, thus, it tends to phase-separate whereas the primary driving force for that is the droplet interfacial free energy. When a surfactant is added, it concentrates at the two immiscible interfaces that imparts a degree of stability by lowering the interfacial tension. Moreover, it prevents immediate droplet recoalescence during preparation.14 Therefore, the interfacial film of the emulsifier is essential for the stability of the product. The film should be sufficiently elastic and form rapidly as soon as droplets are produced, which facilitates the production of microemulsion. Suitable emulsifying agents such as surfactants should be selected. The physical properties of an interface also depend on the pH of the preparation. Therefore, optimum pH has to be maintained for maximum stability.10

**Evaluations of non-aqueous emulsion**

1. *In-vitro* drug release

One of the most common methods used in the study of *in vitro* drug release utilizes a modified diffusion apparatus with dialysis membrane such as drug release study of cytarabine implants.15 The formulations were placed into conical vials open on one side and closed with dialysis membrane on other side and submerged in phosphate buffers pH 7.4 at 37ºC.15 Equal volume of fresh media was replaced to maintain the total volume. Another example was a study of lipophilic drug substances such as H- dexamethasone and H-dehydroepiandrosterone (DHEA) solubilized in castor oil phase and emulsions with different phase volumes were prepared using silicone oil. Each formulation was dialyzed against 100 ml of purified water using a snakeskin dialysis tubing with continual stirring. One hundred microliters of dialysis media was withdrawn at predefined intervals and radioactivity was measured. Sink conditions were maintained throughout the experiment. The equivalent volume of medium was replaced after each sampling procedure.11

2. Stability test

The stability study of emulsions was performed by observing the creaming and breaking behavior over time. The
stability criterion used was the time until breaking: i.e. the time after which 5% of the total amount of oil was floating on the emulsion.\textsuperscript{16,17} The physical and chemical stability study of griseofulvin non-aqueous nanoemulsion are evaluated by agitation test, centrifugation test, freeze-thaw cycles and amount of drug content using UV-visible spectrophotometer.\textsuperscript{18} Typically, the visual observation is the method to analyze the emulsion stability. It can be studied by placing the emulsion in tubes and then stored in ambient conditions. The separation of another phase at the bottom of the container or a complete breakdown into two phases with a layer of surfactant between them is the sign of destabilization.\textsuperscript{14}

The physical stability of non-aqueous in situ PLGA microparticles emulsion was determined by measuring the oil separation as a function of time. In order to screen potential stabilizer with optimized ratio, formulations were stored vertically in 1 ml syringes in a desiccator under ambient conditions.\textsuperscript{19} In process of separation, the oil phase had arisen upward where the solvent moved downward and the rate of solvent separation from the oil phase was calculated. Another example is the assessment of physical and chemical stability of the in situ implants. Stability studies were conducted over the course of 1 month under various storage conditions according to ICH guidelines. Samples containing optimized formulations were placed in vials and stored at 40ºC/75%RH. After 90 days the formulations were inspected for physical appearance and drug content.\textsuperscript{15}

3. Interfacial tension

Interfacial tension is used for the evaluation of the role of surfactants on emulsion systems and interaction behavior between dispersed and continuous phases. The pendant drop method is used by a large number of researches in the determination of interfacial tension. Castor oil containing 5% w/w of each surfactant was slowly formed as a drop in silicone oil at 20ºC. The dimensions of each drop were obtained from digital photographs. De, the equatorial diameter, and Ds, the diameter at the plane at a distance De from the tip of drop were measured. Using the tables reported by Adamson (1990)\textsuperscript{20}, the correlation factor (H) from the shape factor (S=Ds/De) was obtained. Interfacial tension ($\gamma$) was calculated from the following equation.

$$\gamma = \frac{\Delta p \cdot g \cdot De^2}{H}$$

Where $\Delta p$ is density difference between the phases and $g$ is gravitation constant. The method was validated by determining interfacial tension between n-hexane and water.\textsuperscript{4,11}

Another method for the evaluation of surface tension is using the micropipette tensiometry to measure the interfacial tension for individual emulsion droplets containing amphiphilic block copolymers during solvent evaporation.\textsuperscript{21}

4. Pseudo-ternary phase diagram

The emulsification behavior of non-aqueous emulsion systems is completely unpredictable and conventional theories of emulsification and HLB system cannot be applied. Pseudo-ternary phase diagram can be used to facilitate the optimization of non-aqueous emulsions. The pseudo–ternary phase diagram was constructed using titration.\textsuperscript{10}

5. Emulsion droplet size

The diameter of globules is critical factor for creaming of non-aqueous emulsions. Emulsion droplet sizes were investigated by Beckman Coulter counter based on the laser diffraction phenomenon.\textsuperscript{10} The particle size and size distribution were evaluated by laser diffraction measurements and investigated the droplet sizes of the ISM-emulsions under an optical microscope.\textsuperscript{5} The suitable emulsifier should be able to film at the interface between dispersed and continuous phase. The emulsion droplets interface was assessed by determining hot-stage polarized light microscopy, cryo-scanning electron microscopy (Cryo-SEM) and freeze etching-transmission electron microscopy (FE-TEM).\textsuperscript{19}

6. Rheological study viscosity measurement

The flow behavior and viscosity of the non-aqueous emulsions were investigated using a controlled stress mode of the plate and cone device connected with computer interface of a rheometer.\textsuperscript{22}

**Application in pharmaceuticals**

Non-aqueous emulsions are well known as the solvent for drugs, suspension vehicles, oleogels, soft gelatin or magnoresponsive drug delivery system. It provides potential vehicles for lipophilic drugs. Detail of each system is as follows:
1. Oral delivery

Biopharmaceutical classification system (BCS) is a guideline issued by the USFDA, which classified drug substances into different classes based on the three fundamental properties which affect the bioavailability of oral preparations: dissolution, solubility and intestinal permeability. According to BCS, drug substances which have a high permeability, low solubility (BCS class II) and low permeability, low solubility (BCS class IV) are poorly soluble in gastrointestinal fluid. Non-aqueous microemulsions, acting as the super solvent for poorly soluble drugs, can enhance the solubilization of these drugs and overcome the dissolution-related bioavailability problems. A rutin-loaded non-aqueous self-double-emulsifying delivery system (SDEDS) was stabilized by glycerol monostearate and nonionic surfactants. The non-aqueous SDEDS spontaneously formed into oil-in-oil-in-water (O/W) double emulsions in the gastrointestinal environment and improve rutin bioavailability.

2. Topical drug delivery

The stable non-aqueous microemulsion comprising glycerin and mineral oil stabilized by glycerol monostearate with cosurfactant could enhance the dermal penetration/permeation of griseofulvin and drug stability. The use of hydrophobic surfactants was more efficient than hydrophilic surfactant. The emulsion exhibited antifungal activity against Microsporum gypsum with no significant sign of skin irritation on mice skin. Other compounds both hydrophilic (5-fluorouracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate) and lipophilic drugs (estradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide) have reported to be loaded in non-aqueous microemulsion for enhancing their skin permeation. Non-aqueous microemulsion improved the delivery of progesterone, α-tocopherol, and lycopene into viable skin layers. Non-aqueous self-double-emulsifying drug delivery systems (SDEDDS) prepared by mixing the hydrophilic surfactants and oil in oil emulsion could increase aqueous solubility of trans-reveratrol and improve its skin retention.

3. Protein and peptide drug delivery

Designing oral peptides and protein delivery systems has been a persistent challenge to pharmaceutical scientists due to their several unfavorable physicochemical properties including large molecular size, susceptibility to enzymatic degradation, short plasma half-life, ion permeability, immunogenicity, and the tendency to undergo aggregation, adsorption, and denaturation. However, numerous peptides and proteins are identified as novel therapeutic drugs. To circumvent this, non-aqueous microemulsions have been developed and patented for the oral delivery of protein and peptide drugs. Emulsions dosage forms can protect the protein and peptide from chemical and enzymatic breakdown in the intestinal lumen and increase the drug absorption which is dependent on the type of emulsifying agent, particle size of the dispersed phase, pH, solubility of drug, type of lipid phase, etc. The lipid phase of microemulsions comprising medium chain fatty acids triglycerides increased the bioavailability of muramyl dipeptide analog.

4. Magnetic system

The flow of droplets of magnetite nanoparticles in the capillaries can be controlled by designing the magnetite nanoparticles into oil-in-oil emulsion. This feature has drawn much interest especially for the design of microfluidic and pulsatile drug release systems. Application of magneto- and electrorheological systems to achieve a controllable delivery device is an area of research which is gaining interest.

5. Controlled release vehicle

Novel non-aqueous emulsions have the potential to be used as a controlled release system for lipophilic drugs. In addition, the non-aqueous emulsion provides spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, improved drug solubilization of hydrophobic drugs and bioavailability. Therefore, these systems have emerged as the novel vehicles for controlled released drug delivery for percutaneous, oral, topical, transdermal, ocular and parenteral administration of medicaments. The increased local systemic delivery of non-aqueous microemulsions through the skin makes them the suitable vehicles for the delivery of antifungal agents. The intramuscular absorption of this anhydrous microemulsion offers some advantages as the depot or reservoir vehicles for lipophilic drugs in controlled delivery systems. The release profile of dehydroepiandrosterone (DHEA), a highly lipophilic molecule, added to the internal phase of emulsion follows first-order release kinetics. The controlled parenteral drug delivery of novel in situ forming microparticles emulsion has been
reported.\textsuperscript{32} The polymer in the internal phase of ISM emulsion, when contacts with aqueous physiological fluid, forms a depot like matrix by exchange of polar solvents in the emulsion with physiological fluid and subsequently the drug released from this depot in a controlled manner. The drug released from the ISM system decreased when the polymer concentration was increased or the polymer phase: external oil phase ratio was increased. Thus, the type of biocompatible polar solvent affected the drug release.\textsuperscript{32} The six months prolonged leuprolide ISM could be developed by blending poly(lactide-co-glycolide) with different molecular weights.\textsuperscript{33} ISM is suitable for achieving new implant delivery system with low risk of dose-dumping, capable of being modulated to exhibit varying release patterns, reproducible, easily applicable and well tolerated compared with classically surgical implants which Risperidone-ISM\textsuperscript{TM} showed a possibility for prolonged release with intramuscular injection.\textsuperscript{34}

6. Capsules
Regarding the approximately 40\% of new chemical entities that are hydrophobic in nature, the delivery of poorly water-soluble drugs has been the subject of much research. One area in which published literature is lacking is in the field of non-aqueous emulsions filled into capsules. The polyethylene glycol (PEG) has been used as a continuous phase in the preparation of such emulsion.\textsuperscript{35-37} The emulsion comprising low solubility bioactive agents can be filled into hard gelatin as well as soft gelatin capsules. These liquid systems, when administered, subsequently result in the formation of a fine emulsion in the gastric fluid.\textsuperscript{6} This process favors the bioavailability of lipophilic drugs or helps to avoid a mucosal irritation which can be caused by high concentration of administrated drugs. The non-aqueous emulsion is inert toward the capsule shells and did not compromise the seal of these systems over an extended period of time.\textsuperscript{7,10}

7. Periodontal delivery
Aggressive periodontitis, by definition, causes rapid destruction of the periodontal attachment apparatus and the supporting alveolar bone.\textsuperscript{38} It is a major cause of tooth loss. The non-aqueous in situ forming microparticles for treatment of periodontitis provides the advantages of easier injectability through smaller needle sizes,\textsuperscript{22} improved muscle compatibility observed in Sprague Dawley rats\textsuperscript{39,40} and decreased initial burst release of low molecular drugs and peptides in vitro and in vivo.\textsuperscript{5,32,39,41}

Bleached shellac dissolved in biocompatible solvents including N-methyl pyrrolidone (NMP), dimethyl sulphoxide (DMSO) and 2-pyrrolidone was employed as the internal phase of non-aqueous emulsion using olive oil emulsified with glyceryl monostearate (GMS) as the external phase of in ISM.\textsuperscript{12,13,39,42} For periodontitis treatment this doxycycline hyclate-loaded bleached shellac ISM exhibited pseudoplastic flow and notably low injectability force.\textsuperscript{13,42} The transformation from emulsion into microparticles of ISM prepared with 2-pyrrolidone was slow due to slower phase inversion which provoked less porous topography of bleached shellac matrix microparticles. This developed ISM attained a prolonged drug release for 47 days with Fickian diffusion and markedly inhibited \textit{P. gingivalis}, \textit{S. mutans} and \textit{S. aureus} thus it was a suitable formulation for periodontitis treatment.\textsuperscript{12,13,42}

8. Cosmetic preparation
Emulsions comprising organosilicon material are useful in a vast variety of applications and they are primarily intended for personal care usage.\textsuperscript{43} This non-aqueous emulsion intended for cosmetics can be used alone or in combination with cosmetic ingredients. There are a wide variety of uses as cosmetic preparation such as the carriers for antiperspirants and deodorants. It can be used as the lubricant and can improve the desired properties in skin creams, skin care lotions, moisturizers, facial treatments such as acne or wrinkle removers, personal and facial cleansers, bath oils, perfumes, colognes, sunscreens, pre-shave and after-shave lotions, liquid soaps, shaving soaps, and shaving lathers. They can be used in hair shampoos, hair conditioners, hair sprays, mousses, permanents, depilatories, and cuticle coats. Emulsions can also function as leveling and spreading agents for pigments in make-up color cosmetics, foundations, blushes, lipsticks, lip balms, eyeliners, mascaras, oil removers, color cosmetic removers, and powders. When incorporated into sticks, gels, lotions, aerosols, and roll-ons, these emulsions and multiple emulsions produce a dry and silky-smooth feel.\textsuperscript{44}

9. Miscellaneous
Emulsions are also capable of functioning as carriers for pharmaceuticals, biocides, herbicides, pesticides, and other biologically active substances. For further use, they can be
used as additives for cellulose or synthetic nonwoven carrier substrates used in wet-like cleansing wipes such as wet-wipe tissues, and towels, marketed generally for personal hygiene and household cleaning tasks.7,10

The consideration of components used in non-aqueous emulsion should be conducted. The important factor is that the choice of suitable organic polar solvents considering their toxic potential or requirements of newly synthesized emulsifiers that will not comprise the high irritating to the gastrointestinal mucous but exhibit the tissue compatibility. The Food and Drug Administration (FDA) gave approval for gastrointestinal mucous but exhibit the tissue compatibility.

Conclusion

Critical micelle concentration, particle size, viscosity and interface of two phases are physical properties that should be considered in the development of the non-aqueous emulsions. In the pharmaceutical field, this system is developed as the vehicle for hydrophobic drugs or drug susceptible to hydrolysis. Moreover, such systems allow the sustained or controlled release manners. Non-aqueous emulsions have been used for oral and topical drug delivery, protein and peptide drug delivery, periodontal pocket delivery and cosmetic application. Moreover, these systems also have been filled in capsule or used as carrier for magnetite nanoparticles and prepared as the multiple emulsion. Thus, the non-aqueous emulsions have possessed as the potential tool for pharmaceutical applications.

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